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Neurocognitive safety after 96 weeks on dual therapy with atazanavir/ritonavir plus lamivudine: results of the neurocognitive substudy of the SALT randomized clinical trial

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Background: Concerns have been voiced over the capacity of deintensification strategies to preserve neurocognitive function and prevent neurocognitive impairment.

Methods: We present the 96 week results of a neurocognitive substudy nested within the SALT clinical trial: a randomized, open-label, non-inferiority trial that compares whether atazanavir/ritonavir + lamivudine is non-inferior to atazanavir/ritonavir + two NRTIs in HIV-suppressed patients on stable triple therapy. A global deficit score (GDS) for five neurocognitive tasks was used to assess neurocognitive function. Changes in neurocognitive function (GDS value) were determined at weeks 48 and 96. The effect of atazanavir/ritonavir + lamivudine, adjusted for significant confounders, on the change in neurocognitive function was determined using analysis of covariance (ANCOVA) at week 96.

Results: The per-protocol analysis included 92 participants (47 atazanavir/ritonavir + lamivudine and 45 atazanavir/ritonavir + two NRTIs). All baseline characteristics were comparable in both groups. At weeks 48 and 96, changes in GDS [week 48, atazanavir/ritonavir + lamivudine −0.3 (95% CI −0.5 to −0.1) versus atazanavir/ritonavir + two NRTIs −0.2 (95% CI −0.4 to 0.0), $P = 0.39$; week 96, atazanavir/ritonavir + lamivudine −0.3 (95% CI −0.5 to −0.1) versus atazanavir/ritonavir + two NRTIs −0.2 (95% CI −0.4 to −0.1); $P = 0.471$] were similar. This absence of differences was also observed in all cognitive tasks. Atazanavir/ritonavir + lamivudine did not impact the change in neurocognitive function at week 96; the adjusted effect of atazanavir/ritonavir + lamivudine on GDS change, considering atazanavir/ritonavir + two NRTIs as a reference, was 0.01 (95% CI −0.18 to 0.21) ($P = 0.90$).

Conclusions: Neurocognitive function remained stable after 96 weeks, both in the atazanavir/ritonavir + lamivudine and in the atazanavir/ritonavir + two NRTIs arms, provided HIV remained suppressed.

Introduction

The main objective of ART is safe suppression of viral replication. Abacavir/lamivudine or tenofovir/emtricitabine with a third agent are the standard combinations in first-line ART.[1] However, abacavir and tenofovir are associated with drug-related toxicities. Abacavir has been linked in some cohorts with cardiovascular disease,[2] and tenofovir—especially as tenofovir disoproxil fumarate—has been linked with renal and bone toxicity.[3,4]

Several nucleoside-sparing regimens have been tested to avoid abacavir- and tenofovir disoproxil fumarate-related toxicity. Many have failed to demonstrate non-inferiority in the scenarios assessed when compared with standard ART[5,6] and only dual

therapy with lopinavir/ritonavir,[7] atazanavir/ritonavir[8] and darunavir/ritonavir[9] have been proven to be non-inferior to standard triple therapy in maintaining virological suppression.

Lopinavir/ritonavir, darunavir/ritonavir and atazanavir/ritonavir with lamivudine are accepted as alternatives to standard ART for the prevention and treatment of abacavir- and tenofovir disoproxil fumarate-related toxicity.[10] However, while lopinavir/ritonavir and darunavir/ritonavir have good CNS penetration and preserve neurocognitive function, even when administered in monotherapy,[11] there are concerns regarding the capacity of atazanavir/ritonavir + lamivudine to preserve neurocognitive function because levels of atazanavir/ritonavir in CSF are not sufficiently high to suppress replication of HIV in about 20% of patients.[12] Therefore, a study to evaluate the neurocognitive safety of atazanavir/ritonavir + lamivudine is needed.

We performed a subanalysis of the 'Simplification to atazanavir/ritonavir + lamivudine dual therapy versus atazanavir/ritonavir + two nucleos(t)ides in virologically stable patients' (SALT) clinical trial to explore the neurocognitive safety of switching from standard ART to atazanavir/ritonavir + lamivudine.[8]

Patients and methods

Ethics

Clinical Research Ethics Committee of Madrid Region approval was obtained on 7 June 2011 (Ref. 07/450989.9/11) in accordance with the principles of the 2008 Declaration of Helsinki (Seoul, October 2008) and the clinical trial regulation of the European Union (Regulation EU No 536/2014, April 2014) and Spain (RD 1090/2015, December 2015). This approval was ratified by the ethics committee at all participating centres. All participants gave their written informed consent before undergoing any study procedure. Additional written informed consent was required from patients participating in the neurocognitive substudy. The study was registered at ClinicalTrials.gov (NCT01307488) and at EudraCT.ema.europa.eu (2011-001107-12).

Study design, randomization and patients

We performed a neurocognitive substudy nested within the multicentre, randomized, open-label, non-inferiority SALT clinical trial.[8] We included SALT participants who were willing to enrol and fulfilled the selection criteria. The exclusion criteria were active drug consumption affecting activities of daily living, decompensated cirrhosis, active hepatitis C therapy with pegylated interferon, psychomotor alterations, mental retardation, dementia or severe psychiatric disorders (psychosis, bipolar disorder and depression) and active opportunistic illnesses. During the selection process, patients completed the Spanish version of the Hospital Anxiety and Depression (HADS) questionnaire to rule out depression.[13] Patients with a score >9 were considered to have depression and were also excluded.

Procedures

Patients were assessed at baseline, week 48 and week 96. At each visit, neurocognitive assessments were performed following the American Association of Neurology 2007 recommendations for diagnosis of HIV-associated neurocognitive disorders.[14] To assess neurocognition we used a battery of five tests that included Trail Making Test A (TMT-A), Trail Making Test B (TMT-B), Digit Symbol Test (DST) and Grooved Pegboard Test (GPT) with both the dominant and non-dominant hands. With these tests we assessed mental flexibility, speed of information processing, fine motor skills, attention span and working memory. We did not use a more extensive battery of tests because we tried to maximize the number of patients who completed the protocol, avoiding losses due to lack of time for longer visits.

The raw scores obtained in each test were converted into demographically adjusted T-scores using the best available normative standards for Spanish populations (TMT-A, TMT-B and DST).[15] For the GPT, normative data for Spanish populations are not available.[16] Test results were considered normal if scores were above 1 SD below the mean and impaired for scores below 1 SD below the mean. Global neurocognitive performance was estimated using a global deficit score (GDS).[17] GDS was preferred to clinical ratings or other modalities of neuropsychological testing because it provides a continuous measure of neurocognitive performance and it is more specific in detecting changes in neurocognitive performance.

Outcomes and statistical analysis

Our primary objective was to compare the effect on neurocognitive function, after 96 weeks, of switching to atazanavir/ritonavir + lamivudine (dual therapy) with that of switching to atazanavir/ritonavir + two NRTIs (standard triple therapy). Our secondary objective was to compare patients who switched to atazanavir/ritonavir + lamivudine versus with those who switched to atazanavir/ritonavir + two NRTIs in terms of neurocognitive performance overall and by ability domains at baseline, week 48 and week 96. The study was conducted in the per-protocol population. Participants who failed to complete all study procedures were excluded from the analyses.

Continuous variables were expressed as mean and SD when normally distributed and as median and IQR when non-normally distributed. Discrete variables were expressed as percentages. We used an independent samples *t*-test to compare continuous variables and the Mann–Whitney test to compare non-normally distributed continuous variables. The association between categorical variables was evaluated using the χ^2 test when samples were of sufficient size or with the Fisher's exact test when they were not. Neurocognitive change (GDS at week 96 minus GDS at baseline) was assessed using analysis of covariance (ANCOVA).

We evaluated our primary objective using two methods. First, we applied ANCOVA to estimate the effect (fitted by linear regression) of receiving dual therapy on GDS at week 96, adjusted for GDS at week 48 and baseline, using the standard-triple-therapy group as a reference. This result was then adjusted for neurocognitive confounders that changed the association between dual therapy and follow-up GDS by $\geq$20%. These confounders were age, gender, ethnicity, route of HIV transmission, years on ART, years since HIV diagnosis, years of HIV suppression, CD4 nadir and current counts, years of education, AIDS-defining conditions, presence of comorbidities (neurological, medical or psychiatric), hepatitis C coinfection, previous use of atazanavir and cholesterol/HDL ratio.

Second, to analyse sensitivity, we fitted a linear regression model directly over the values of change in GDS. The first method has the advantage of providing a more accurate estimator, thus preventing the bias known as regression to the mean. All tests were two-sided and differences were considered significant at $P < 0.05$.

Results

A total of 171 patients agreed to participate in the neurocognitive substudy (59.8% of the 286 participants in the SALT trial; Figure S1, available as Supplementary data at *JAC* Online). Patients who agreed to participate in the substudy were younger (mean age, 42.3 versus 46.6 years; $P < 0.001$), had spent longer in education (mean, 13.0 versus 10.5 years; $P = 0.002$), had lived with HIV for a shorter period (median, 5.3 versus 7.3 years; $P = 0.017$), had been exposed to ART for a shorter period (median, 37.7 versus 40.8 months; $P = 0.035$) and had suppressed HIV for a shorter period (median, 26 versus 31 months; $P = 0.027$) than the patients enrolled in the SALT trial who refused to participate in the substudy.

Table 1. Patient characteristics at baseline

Characteristic	ATV/r + 3TC ($n = 47$)	ATV/r + two NRTIs ($n = 45$)	*P* value
Age, mean (SD), years	42 (10.1)	42 (7.7)	0.939
Female gender, *n* (%)	12 (25.5)	8 (17.8)	0.452
Born in Spain, *n* (%)	37 (78.7)	36 (80)	0.494
Time in education, mean (SD), years	13.3 (5.2)	13.9 (5.2)	0.558
Neurological comorbidities, *n* (%)	2 (4.3)	5 (11.1)	0.262
Psychiatric comorbidities, *n* (%)	23 (48.9)	25 (55.6)	0.539
Cardiovascular comorbidities, *n* (%)	26 (55.3)	22 (48.9)	0.677
Atherogenic index, median (IQR)	3.9 (3.4–4.6)	3.9 (3.4–4.6)	0.906
HCV RNA-positive, *n* (%)	6 (12.8)	7 (15.6)	0.771
Previous AIDS-defining illness, *n* (%)	15 (31.9)	13 (28.9)	0.823
Risk behaviour for HIV infection, *n* (%)			
sexual relations	36 (76.6)	39 (86.7)	
IVDU	10 (21.3)	4 (8.9)	0.205
other	1 (2.1)	2 (4.4)	
Known duration of HIV infection, median (IQR), years	6.5 (3.2–10.0)	6.1 (3.4–10.7)	0.941
Nadir CD4 count, cells/mm^3, median (IQR)	218 (70–309)	184 (105–300)	0.950
Baseline CD4 count, cells/mm^3, median (IQR)	633 (440–796)	581 (405–802)	0.714
Months of ART prior to study entry, median (IQR)	38.3 (26.2–58.6)	46.5 (21.5–70.2)	0.734
Months of HIV suppression prior to study entry, median (IQR)	26 (17–47)	37 (14.5–62.5)	0.319
Switched to treatment including (%):			
NNRTI	16 (34)	15 (33.3)	0.999
boosted PI	28 (59.6)	28 (62.2)	0.833
ABC	8 (17)	8 (17.8)	0.999

ATV/r, atazanavir/ritonavir; 3TC, lamivudine; ABC, abacavir.

Seventy-nine patients (46.2%) did not complete all the substudy procedures and therefore were excluded from the per-protocol analyses. Reasons why these patients failed to complete the study procedures were: lost to follow up (13 patients on atazanavir/ritonavir + lamivudine and 8 on atazanavir/ritonavir + 2 NRTIs), discontinuation owing to adverse events (4 and 5 patients, respectively); virological failure (5 and 7 patients, respectively) and an incomplete neurocognitive evaluation at weeks 48 and/or 96 (16 and 19 patients, respectively).

Ninety-two patients (53.8%) completed all the substudy procedures and were evaluated in the per-protocol analyses. The baseline characteristics of these patients, including neurocognitive performance, were similar to those of patients who did not complete the study procedures, with one exception: the percentage of patients coinfected with hepatitis C was higher in patients who did not complete the study protocol (30.4% versus 14.1%; $P = 0.015$). The per-protocol population included 47 patients randomized to switch to dual therapy and 45 patients randomized to switch to standard triple therapy. The baseline characteristics were similar in both study arms (Table 1).

Global neurocognitive performance at baseline, week 48 and week 96 was similar for dual therapy and standard triple therapy (Table 2). Neurocognitive performance by ability to perform tests from the battery was also similar between study arms at all visits (Figure 1).

Results of the primary and sensitivity analyses of the main study objective are also reported in Table 2. In the primary analysis (per population, the effect of dual therapy on GDS at week 96 adjusted for GDS at baseline and week 48), considering standard triple therapy as the reference, dual therapy with atazanavir/ritonavir + lamivudine did not affect the change in GDS [0.012 (95% CI −0.182 to 0.206); $P = 0.903$]. Significant neurocognitive confounders did not affect this result because none of them had an impact higher than 20% on GDS at week 96. Similar results ($P = 0.691$) were observed in the sensitivity analysis when the change in GDS at week 96 was compared between the dual-therapy arm [−0.287 (95% CI −0.443 to −0.131)] and the standard-triple-therapy arm [−0.242 (95% CI −0.402 to −0.083)].

The effect of dual therapy on the change in raw performance at week 96 using standard triple therapy as a reference was also evaluated using ability tasks (Table 3). The effect size of dual therapy on changes in neurocognitive raw scores was small for all tasks.

Patients whose neurocognitive functioning improved (GDS at week 96 minus GDS at baseline <0) were compared with patients whose neurocognitive functioning did not. Globally, there were no differences. By treatment group, patients receiving triple therapy whose neurocognition improved were younger (mean age, 40.6 versus 45.4 years; $P = 0.036$) and were less likely to have had an AIDS-defining condition (12.5% versus 47.6%; $P = 0.009$). No differences were observed between patients receiving dual

Table 2. Neurocognitive performance and neurocognitive changes at baseline, week 48 and week 96 and impact of dual therapy on change in GDS at week 96

Neurocognitive measurement	ATV/r + 3TC ($n = 47$)	ATV/r + two NRTIs ($n = 45$)	*P* value
GDS at baseline, median (IQR)	1.2 (0.9–1.5)	1.1 (0.8–1.5)	0.802
GDS at week 48, median (IQR)	0.9 (0.6–1.1)	1.0 (0.6–1.3)	0.844
GDS at week 96, median (IQR)	0.9 (0.6–1.1)	0.9 (0.6–1.1)	0.987
GDS change from baseline to week 48, mean change (95% CI)	−0.30 (−0.46 to −0.14)	−0.18 (−0.35 to −0.02)	0.327
GDS change from baseline to week 96, mean change (95% CI)	−0.29 (−0.44 to −0.13)	−0.24 (−0.40 to −0.08)	0.691
Effect of dual therapy on change in GDS at week 96[a], mean change (95% CI)	0.01 (−0.18 to 0.21)	reference	0.903

ATV/r, atazanavir/ritonavir; 3TC, lamivudine.
[a]Adjusted for GDS at baseline, GDS at week 48 and significant confounders (none) and using the standard triple therapy as a reference.

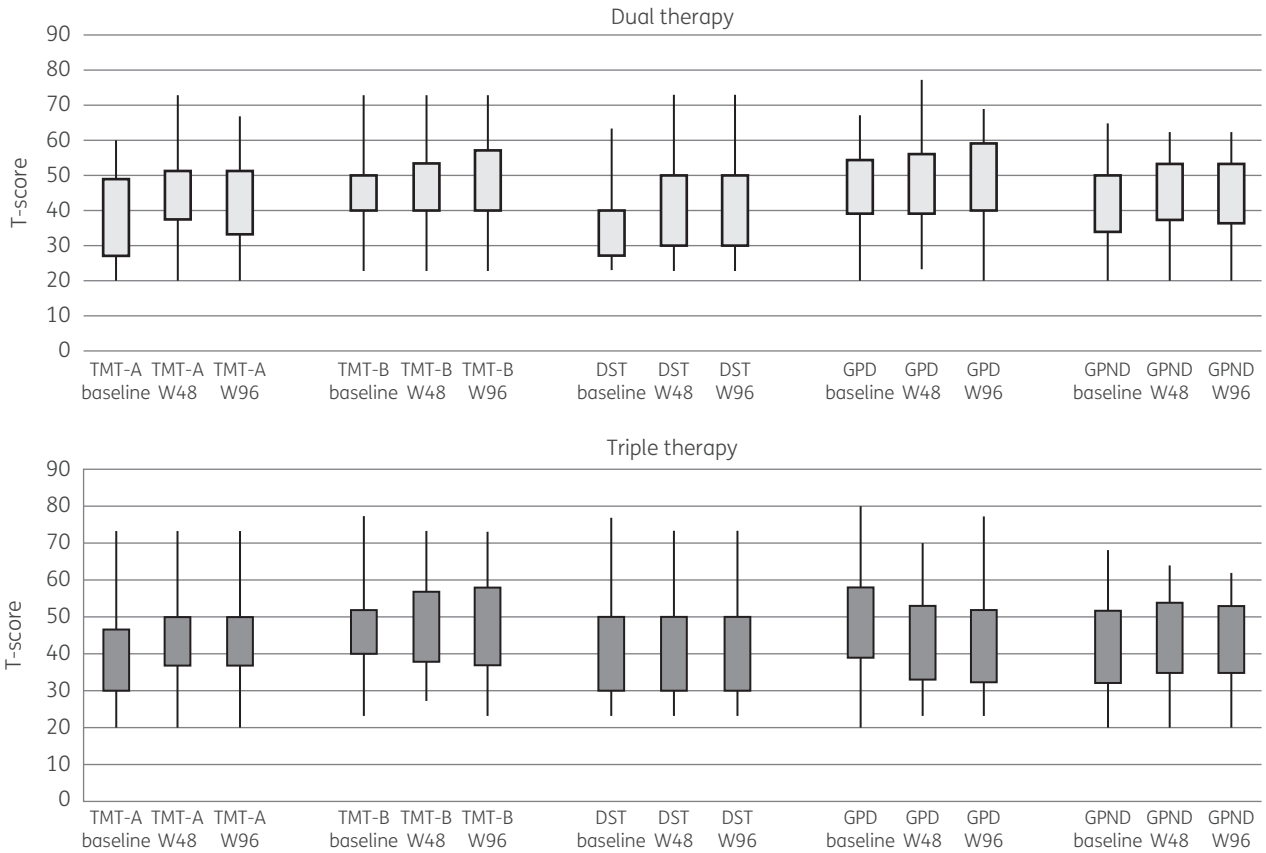

Figure 1. Neurocognitive performance by ability to perform tasks. DST, digit symbol test; GPD, grooved pegboard dominant hand; GPND, grooved pegboard non-dominant hand; W48, week 48; W96, week 96.

therapy whose neurocognitive functioning improved and those whose neurocognitive function did not (Table S1).

Discussion

We performed the first prospective substudy nested within a randomized clinical trial that has evaluated the neurocognitive safety of deintensifying treatment to dual therapy in patients with suppressed HIV replication taking standard triple therapy. Dual therapy with atazanavir/ritonavir + lamivudine had a similar impact on neurocognitive performance to standard triple therapy with atazanavir/ritonavir + two NRTIs after 96 weeks of follow-up. This result was consistent across several sensitivity analyses. After 96 weeks, neurocognitive function remained stable in both arms.

No previous studies have evaluated the neurocognitive function of aviraemic patients taking dual therapies. Our results are supported by other deintensification studies reporting similarly stable neurocognitive function in aviraemic patients switching to PI monotherapy or triple therapy. Four clinical trials have compared changes in neurocognitive function in aviraemic patients

Table 3. Effect sizes of dual therapy on changes (from baseline to week 96) in the raw scores obtained in each ability task

Score	ATV/r + 3TC	ATV/r + two NRTIs	Cohen's d	r
TMT-A raw score change from BL to week 96, mean change (SD)	−8.28 (16.87)	−6.31 (16.36)	0.119	0.059
TMT-B raw score change from BL to week 96, mean change (SD)	−12.06 (20.63)	−7.57 (30.63)	0.172	0.086
DST raw score change from BL to week 96, mean change (SD)	4.83 (8.79)	1.22 (13.11)	−0.323	−0.160
GPD raw score change from BL to week 96, mean change (SD)	−3.11 (10.43)	−3.03 (11.82)	0.007	0.004
GPND raw score change from BL to week 96, mean change (SD)	−0.76 (12.16)	−4.96 (16.46)	−0.290	−0.144

DST, digit symbol test; GPD, grooved pegboard dominant hand; GPND, grooved pegboard non-dominant hand; ATV/r, atazanavir/ritonavir; 3TC, lamivudine; BL, baseline.

switching to PI monotherapy or continuing on standard triple therapy.[18–21] Two of them included patients who received atazanavir/ritonavir monotherapy.[19,20] In addition, one longitudinal study performed a detailed comparison of the change in performance of seven neurocognitive domains commonly affected by HIV infection in aviraemic patients on monotherapy or triple therapy.[22]

In the PIVOT clinical trial, the change in neurocognitive performance (NPZ-5) was similar after 44 months in aviraemic patients who switched to any PI monotherapy or maintained standard triple therapy.[19] In the pilot MODAt trial, the change in neurocognitive performance (NPZ-8) was also similar after 96 weeks in aviraemic patients switching to atazanavir/ritonavir monotherapy or continuing on standard triple therapy.[20] In the MOST and PROTEA trials, the change in neurocognitive performance (NPZ-5) was also similar after 48 weeks in aviraemic patients switching to lopinavir/ritonavir or darunavir/ritonavir, respectively, when compared with aviraemic patients continuing on standard triple therapy.[18,21] Furthermore, in the more detailed neurocognitive evaluation performed in the PICASSO study, neurocognitive stability was observed in all the ability domains, even though patients were treated with one or three antiretrovirals.[22]

In viraemic patients, only the NEAT-001 clinical trial has performed longitudinal follow-up of neurocognitive function in patients starting dual therapy. In this study, patients starting ART with darunavir/ritonavir + two NRTIs and patients starting dual therapy with darunavir/ritonavir + raltegravir showed similar improvement in their neurocognitive function.[23] This result suggests that to achieve HIV suppression, it is more important to improve and preserve neurocognitive function than the number of antiretrovirals used for that purpose. The neurocognitive safety results of the NEAT-001 and the SALT trials are very relevant for the acceptance of ongoing new dual-therapy strategies with dolutegravir and cabotegravir.

Consistent with the findings of these clinical trials and longitudinal studies, our results suggest that in patients who have durable virological suppression in the blood, the number of antiretroviral drugs included in the regimen does not affect neurocognitive function. Furthermore, our results contradict those of previous cross-sectional and longitudinal studies, which questioned the capacity of deintensification therapies to protect neurocognitive function and suggested that the risk of neurocognitive impairment[24,25] and CSF viral escape[26] was higher in patients who receive regimens including a limited number of antiretrovirals with good CSF penetration and effectiveness (CPE) rankings.

There are some studies that have found an association between worse changes in neurocognitive function and lower CPE ranks. All of them included a proportion of patients without virological suppression in the blood.[26,27] We believe this is a critical factor that would explain why the CPE rank was not effective for predicting neurocognitive impairment in deintensification studies that only included aviraemic patients. In our opinion, the neurocognitive benefits of durable virological suppression in the blood offset the potential negative impact of using ART regimens including a limited number of drugs with good CPE.

We support our opinion with the fact that in the CPE rank validation, HIV suppression in the blood was a stronger predictor of CSF HIV suppression than the CPE rank itself;[26] and with the fact that in the CHARTER cohort, the CPE rank did not predict changes in cognitive function, whereas the levels of HIV viral load in the plasma were associated with neurocognitive decline and recovery (high and low viral loads respectively).[28]

There are several alternative hypotheses to explain why deintensification therapies do not have a negative impact on the change in neurocognitive performance. A meta-analysis of 23 studies suggested that the beneficial effect of ART on neurocognition is no more than a consequence of the capacity of ART to ensure recovery of immune function.[29] If this suggestion proves to be true, the type of ART might have little effect on neurocognition.

Another hypothesis to explain the favourable cognitive profile of deintensification therapies may be associated with a reduction of ART-related neurotoxicity. *In vitro* studies have demonstrated that abacavir and tenofovir produce neurotoxicity to a greater or lesser extent.[30] Abacavir has also been associated with higher risk of cerebrovascular events and,[31] in animal models, with increased neuronal β-amyloid production and a marked decrease in the ability of microglial cells to phagocytose β-amyloid.[32] In addition, abacavir may interfere with mitochondrial DNA synthesis, especially when it is administered in combination with other NRTIs.[33] Meanwhile, tenofovir has been associated with mitochondrial and telomere toxicity[34] and high CSF to plasma ratios with worse neurocognition.[35]

Our study has several limitations. First, not all the patients enrolled in the SALT trial enrolled in this substudy and completed all of its procedures. As the sample analysed was relatively small, a type II error cannot be excluded. In addition, patients who refused to participate were older, worse educated, and had been exposed to HIV and ART for a longer time. Since these factors have been associated with cognitive function decline and/or impairment, we cannot exclude a worse neurocognitive performance in the

subgroup of patients who refused to participate in the substudy. However, considering the high similarity observed in both arms of our trial, we do not expect large differences in neurocognitive performance between the two regimens, even if the proportion of patients with neurocognitive impairment had been higher.

Second, in our statistical model, we assumed that the effect of dual therapy on neurocognitive change was constant over time but it is possible that the effect might be episodic.

Third, we cannot exclude the possibility that longer follow-up will be necessary to find differences in the change in neurocognitive function. This possibility is unlikely, however, since other studies with a similar follow-up period reported significant changes in neurocognitive functioning,[20–22] as did other deintensification studies with a longer follow-up period.[19]

Fourth, unfortunately, we did not evaluate CSF. Several studies have shown that atazanavir and lamivudine both have a poor CSF/IC_{50} ratio.[12,36] Therefore we cannot be sure that the combination of atazanavir + lamivudine is able to prevent CSF HIV escape. In relation to this possibility, none of our patients developed acute encephalitis, as was the case in patients receiving monotherapy or triple therapy who presented with CSF virological failure. In addition, a small pilot study reported similar rates of CSF HIV escape with atazanavir/ritonavir monotherapy than with conventional triple therapy.[37,38]

Finally, we used a brief battery of tests and we did not correct our results by the learning effect. Therefore, the GDS results observed at weeks 48 and 96 were limited to a reduced number of neurocognitive functions and could slightly overestimate neurocognitive function. However, it is unlikely that this last factor would affect the comparison of GDS change between groups.

Our study results are relevant because they indicate that deintensification to dual therapy with atazanavir/ritonavir + lamivudine in aviraemic patients is associated with a safe neurocognitive profile, even though both drugs have an average CPE ranking. This observation is particularly true if we consider that atazanavir/ritonavir + lamivudine has been accepted in some clinical guidelines as an alternative to standard triple therapy for preventing and treating NRTI-related toxicities.[19]

In conclusion, after two years of follow-up, deintensification to atazanavir/ritonavir + lamivudine to maintain suppression of HIV in blood does not appear to be associated with a worse change in neurocognitive function or higher incidence of neurocognitive deterioration than standard triple therapy. Our findings reinforce the idea that CPE rank classification might not be applicable to aviraemic patients receiving deintensified ART.

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Author contributions

All authors have made substantial contributions to conception and design, acquisition of data and/or analysis and interpretation of data. All authors participated in drafting the article and revising it critically for important intellectual content. All authors gave final approval of the version to be submitted any revised versions.

Supplementary data

Table S1 and Figure S1 appear as Supplementary data at *JAC* Online.

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